

**Amendments to the claims:**

This listing of claims replaces all prior versions, and listings, of claims in the application.

**Listing of claims:**

Claims 1-76 (canceled).

77. (Currently amended) A modified human TNF $\alpha$  molecule capable of raising neutralizing antibodies towards wild-type human TNF $\alpha$  following administration of said modified TNF $\alpha$  molecule to a human host, wherein at least one segment of the human TNF $\alpha$  molecule has been substituted by at least one peptide containing an immunodominant T cell epitope or a truncated form of said molecule containing an immunodominant T-cell epitope and one or both flanking regions of the human TNF $\alpha$  molecule comprising at least one TNF $\alpha$  B cell epitope, wherein the substitution is introduced in any one of the strands of the front  $\beta$ -sheet, in any one of the connecting loops or in any one of the B', I, or D strands of the back  $\beta$ -sheet, or in any one of the connecting loops and in any one of the B', I, or D strands of the back  $\beta$ -sheet, and which substitution leads to inactivation of the biological activity of human TNF $\alpha$  and which substitution essentially ensures preservation of the  $\beta$ -sheet structures of the B and G strands.
- 78 (Previously presented) The human TNF $\alpha$  molecule according to claim 77, wherein the substitution does not comprise any complete strand of the back  $\beta$ -sheet.

Claim 79. (cancelled)

80. (Currently amended) The human TNF $\alpha$  molecule according claim 77, wherein the substitution comprises at least a segment of the H strand of the front  $\beta$ -sheet and of the connecting loop to the I strand of the back  $\beta$ -sheet, or a segment of the H and I strands and the entire connecting loop, or a segment of the D strand of the back  $\beta$ -sheet and at least a segment of the E strand of the front  $\beta$ -sheet and the entire connecting loop, or the entire C' and C strands of the front  $\beta$ -sheet and a segment of the D strand of the back  $\beta$ -sheet, or at least a segment of the E strand of the front  $\beta$ -sheet and of one or both the connecting loops.
81. (Previously presented) The human TNF $\alpha$  molecule according to claim 77, wherein the substitution has been made in regions of the TNF $\alpha$  molecule which involves the strands of the front  $\beta$ -sheets and/or the connecting loops so as to essentially preserve the  $\beta$ -sheet structure of any of the strands of the back  $\beta$ -sheet.
82. (Previously presented) The human TNF $\alpha$  molecule according to claim 80, wherein the substitution has been made in regions of the TNF $\alpha$  molecule, which involve a segment of the D strand of the back  $\beta$ -sheet.

83. (Previously presented) The human TNF $\alpha$  molecule according to claim 80, wherein the substitution comprises at least a segment of the H strand of the front  $\beta$ -sheet and of the connecting loop to the I strand.
84. (Previously presented) The human TNF $\alpha$  molecule according to claim 80, wherein the substitution comprises segments of the H and I strands and the entire connecting loop.
85. (Previously presented) The human TNF $\alpha$  molecule according to claim 80, wherein the substitution comprises a segment of the D strand, at least a segment of the E strand and the entire connecting loop.
86. (Previously presented) The human TNF $\alpha$  molecule according to claim 80, wherein the substitution comprises the entire C' and C strands and a segment of the D strand.
87. (Previously presented) The human TNF $\alpha$  molecule according to claim 80, wherein the substitution comprises at least a segment of the E strand and of the front  $\beta$ -sheet of one or both of the connecting loops.

88. (Previously presented) The TNF $\alpha$  molecule according to claim 77, wherein when said modified TNF $\alpha$  molecule is tested for biological activity in the L929 bioassay, it is substantially free from TNF $\alpha$  activity.
89. (Currently amended) The TNF $\alpha$  molecule according to claim 77, wherein neutralizing antibodies raised against said modified TNF $\alpha$  molecule in a suitable host is able to significantly inhibit the activity of native TNF $\alpha$  in the L929 bioassay, and/or wherein said antibodies significantly inhibit the binding of wild-type human TNF $\alpha$  to the 55 kD TNF $\alpha$  receptor 1 (TNF $\alpha$ -R55) or ~~the~~ to the 75 kD TNF $\alpha$  receptor (TNF $\alpha$ -R75).
90. (Currently amended) The human TNF $\alpha$  molecule according claim 77, wherein the inserted T cell epitope is promiscuous and ~~known to be~~ immunogenic in a majority of human HLA class II types.
91. (Currently amended) The human TNF $\alpha$  molecule according to claim 90, wherein the epitope is ~~derived~~ from Tetanus toxoid.
92. (Previously presented) The human TNF $\alpha$  according to claim 91, having the amino acid sequence shown in SEQ ID NO:8.

93. (Previously presented) The human TNF $\alpha$  according to claim 91, having the amino acid sequence shown in SEQ ID NO:10.
94. (Previously presented) The human TNF $\alpha$  molecule according to claim 91, having the amino acid sequence shown in SEQ ID NO:4 or SEQ ID NO:16.
95. (Previously presented) The human TNF $\alpha$  according to claim 91, having the amino acid sequence shown in SEQ ID NO:20.
96. (Previously presented) The human TNF $\alpha$  according to claim 91, having the amino acid sequence shown in SEQ ID NO:14.
97. (Previously presented) Dimers, oligomers or multimers of the human TNF $\alpha$  molecule according of claim 77.
98. (Previously presented) An isolated DNA molecule that codes for a human TNF $\alpha$  molecule according of claim 77.
99. (Previously presented) A vector which comprises the isolated DNA molecule according to claim 98.

100. (Previously presented) An expression vector, which comprises the isolated DNA molecule according to claim 98 operatively linked to an expression control sequence.
101. (Previously presented) A host, which is transformed with the expression vector of claim 100.
102. (Previously presented) A host according to claim 101, which host is a strain of bacteria or fungi or an insect, mammalian, or avian cell line.
103. (Previously presented) A method of producing a human TNF $\alpha$  molecule comprising growing the host cells of claim 101 under suitable conditions permitting production of the human TNF $\alpha$  and recovering the human TNF $\alpha$  so produced.
104. (Previously presented) The human TNF $\alpha$  molecule according to claim 77 in the form of a fusion protein with an adjuvant molecule.
105. (Previously presented) A vaccine against TNF $\alpha$ , comprising an immunogenic amount of one or more human TNF $\alpha$  molecules according to claim 77 in combination with a pharmaceutically acceptable excipient and optionally a pharmaceutically acceptable adjuvant.

106. (Previously presented) A vaccine according to claim 105 for the prevention or treatment of diseases promoted by  $\text{TNF}\alpha$  release or activity.
107. (Previously presented) A vaccine against  $\text{TNF}\alpha$  comprising isolated DNA coding for the human  $\text{TNF}\alpha$  molecule according to claim 77 inserted in an expression vector.
108. (Previously presented) A vaccine according to claim 107 containing a construct comprising a non-infectious non-integrating DNA sequence encoding the human  $\text{TNF}\alpha$  molecule according to claim 77 operatively linked to a promoter sequence that controls the expression of said DNA sequence in humans, in an amount sufficient that uptake of said construct occurs, and sufficient expression occurs to induce a neutralizing antibody response against  $\text{TNF}\alpha$ .
109. (Previously presented) A vaccine according to claim 107, wherein the expression vector is a viral expression vector
110. (Previously presented) A vaccine according to claim 105 formulated for oral or parenteral administration.

111. (Previously presented) A method comprising raising antibodies against a human TNF $\alpha$  molecule by administering to a human the a vaccine as defined in claim 105 and using the antibodies in a diagnostic in vitro test for TNF $\alpha$ .
112. (Previously presented) In a diagnostic in vitro method of using antibodies raised against a human TNF $\alpha$  molecule, the improvement wherein the TNF $\alpha$  molecule is the human TNF $\alpha$  molecule according to claim 77.
113. (Previously presented) A method of testing human body fluids for the presence of TNF $\alpha$  which comprises contacting a composition containing antibodies raised against the human TNF $\alpha$  molecule according to claim 77 with a sample of human body fluid and determining whether said antibodies bind to TNF $\alpha$  in said sample.
114. (Previously presented) A method for diagnosing TNF $\alpha$ -related diseases employing an in vitro immunoassay to detect TNF $\alpha$  in human body fluids.
115. (Previously presented) The method of claim 113 wherein the testing uses a sandwich assay or ELISA assay, unamplified or amplified.



116. (Previously presented) A method of manufacture of a medicament for the treatment or prevention of diseases in human beings, the pathophysiology of which is at least partially due to TNF $\alpha$  release or activity, comprising combining an effective amount of at least one human TNF $\alpha$  molecule according to claim 77 with pharmaceutically acceptable a adjuvant or carrier molecule.
117. (Previously presented) The human TNF $\alpha$  molecule according to claim 104, wherein the adjuvant molecule is an immunologically active adjuvant.
118. (Previously presented) The human TNF $\alpha$  molecule according to claim 104, wherein the adjuvant molecule is GM-SCF, HSP70, or interleukin.
119. (Previously presented) A vaccine according to claim 105, wherein the pharmaceutically acceptable adjuvant is aluminum phosphate, aluminum hydroxide, calcium phosphate, muramyl dipeptide, or iscom.
120. (Previously presented) A vaccine according to claim 106, wherein the diseases are chronic inflammatory diseases, cancer, disseminated sclerosis, diabetes, psoriasis, osteoporosis, or asthma.

121. (Previously presented) A vaccine according to claim 120, wherein the chronic inflammatory diseases are rheumatoid arthritis or inflammatory bowel diseases.
122. (Previously presented) A vaccine according to claim 121, wherein the inflammatory bowel diseases are Crohn's disease or Colitis Ulcerosa.
123. (Previously presented) A vaccine according to claim 109, wherein the viral expression vector is a retroviral expression vector.
124. (Previously presented) A vaccine according to claim 110, wherein the vaccine is formulated for subcutaneous, intramuscular, or intradermal administration.
125. (Previously presented) The method according to claim 111, wherein the antibodies are monoclonal antibodies.
126. (Previously presented) The method of claim 115, wherein the assay is amplified using avidin/biotin conjugation.

127. (Previously presented) The human TNF $\alpha$  molecule according to claim 83, wherein the segment of the H strand of the front  $\beta$ -sheet and of the connecting loop to the I strand is the segment of amino acids 132 to 146.
128. (Previously presented) The human TNF $\alpha$  molecule according to claim 84, wherein the segment of the H and I strands and the entire connecting loop is the segment of amino acids 132 to 152
129. (Previously presented) The human TNF $\alpha$  molecule according to claim 85, wherein the segment of the D strand, at least a segment of the E strand and the entire connecting loop is the segment of amino acids 65 to 79 or 64 to 84.
130. (Previously presented) The human TNF $\alpha$  molecule according to claim 86, wherein the entire C' and C strands and a segment of the D strand is the segment of amino acids 40 to 60.
131. (Previously presented) The human TNF $\alpha$  molecule according to claim 87, wherein the segment of the E strand and of the front  $\beta$ -sheet of one or both of the connecting loops is the segment of amino acids 76 to 90.

132. (Previously presented) The human TNF $\alpha$  molecule according to claim 91, wherein the epitope is epitope P2 and/or P30.